

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant(s) : Oleg Iliich Epshtein  
Title of Invention : Media and method for treating pathological syndrome  
Date Filed : January 22, 2005  
Serial No. : 10/522,652  
Examiner : WEN, Sharon X  
Art Unit : 1644  
Confirmation No. : 8482

**DECLARATION UNDER 37 CFR 1.132**

I, O. I. Epshtein, Dr. Sc, do hereby declare as follows:

1. My name is Dr. Oleg I. Epstein (aka Epshtein). I am a widely recognized scientist in the fields of pharmacology and physiology. I authored over 100 articles in the peer-reviewed journals.

2. The company I lead, Materia Medica Holdings, successfully sells the product covered by the above-identified application 10/522,652. I am the inventor of the '652 application.

3. Attached herewith as an Exhibit I is a Report entitled *Determination of Ultra-Low Doses of Antibodies to Interferon Gamma Antiviral Efficacy After Intranasal Challenge, with a Lethal Dose of Influenza A Virus in BALB/C Mice* prepared by APcis, an outside vendor retained by Materia Medica to conduct an independent evaluation of the effectiveness of Materia Medica's preparation of homeopathic form of antibodies to gamma interferon. The substance of the report is incorporated by reference herein and discussed below in brief.

4. The mice were divided into 4 Groups of 20. Mice in Groups 1-3 were exposed to individual inoculation with Influenza hemagglutinating virus H3N8 via intranasal route. Subsequent to the introduction of the virus, the mice of Group 1 were treated with a mixture of homeopathic dilutions (C12, C30, and C50) of antibodies to interferon gamma; the mice in Group 2 were treated with oseltamivir (TAMIFLU); the mice in Group 3 were treated with placebo. The mice in Group 4 were not challenged by the virus and were left untreated. The study design is set forth in the Table below (Report, 3.2):

<b>Days of experiment</b>	1-5	6	7-11	12-32
<b>Days after challenge</b>	(-5)-(-1)	(0) Day of challenge Time of challenge is 11.00 ±1 hr	(1)-(5)	(6)-(26)

<b>Group 1 Test article group (20 mice)</b>	Ultra low doses of antibodies to interferon gamma by oral gavages twice daily (0.2 ml/ mouse per gavage) at 10.00± 1hr and 17.00± 1hr.		
<b>Group 2 Reference group (20 mice)</b>	Placebo by oral gavages twice daily (0.2 ml/ mouse per gavage) at 10.00± 1hr and at 17.00± 1hr	Oseltamivir by oral gavages twice daily at 10.00 ± 1hr and at 17.00 ± 1hr. with first treatment just after challenge (1 hour)	Placebo by oral gavages twice daily (0.2 ml/ mouse per gavage) at 10.00 ± 1hr and at
<b>Group 3 Untreated challenges control group (20)</b>	Placebo by oral gavages twice daily (0.2 ml/ mouse per gavage) at 10.00± 1 hr and 17.00± 1 hr.		
<b>Group 4 Negative control Group (20)</b>	Unchallenged and untreated group. Received no treatment and no inoculum to monitor reference untreated growth and health patterns.		

5. The primary criterion of effectiveness was the mean life duration to mortality. The results of the study are set forth in the Table below (Report, 4.2):

<i>Group</i>	<i>Products</i>	<i>Mean life duration</i>
Group 1	ULD of Ab to IFN	25.05±0.95
Group 2	Oseltamivir	21.65±1.76
Group 3	Placebo	13.55±1.69
Group 4	Unchallenged	26.00±0.00

6. In my opinion, the results of the APCis study clearly support a conclusion that a preparation based on homeopathic dilution of antibodies to interferon is statistically far more effective than placebo ( $p < 0.001$ ). It is also my opinion that a preparation based on homeopathic dilution of antibodies to interferon is at least as effective or more effective in treating influenza as oseltamivir, a well-known pharmaceutical compound used in the treatment of influenza.

7. It is also my understanding the Examiner requested a showing that the terms "homeopathic," "homeopathic dilution," "homeopathic potentization", and "C12 or C30" were recognized in the art at the time the '652 application was filed.

8. Attached herewith as Exhibit II is an excerpt from a published English language translation of German Homoeopathic Pharmacopoeia (GHP) (1991). GHP is a voluminous, standard reference text on homeopathy. The attached Exhibit II includes the i) the title page, ii) the

content page, iii) a page from the section entitled "Formulations and Presentations," and iv) a portion of the monograph entitled "Manufacture."

9. In the section of the attached Exhibit II entitled Formulations and Presentations, the GHP teaches:

Liquid formulations are mother tinctures and solutions, as well as liquid dilutions of these; solid formulations are triturations of these (triturations). Different concentrations of these formulations (degrees of dilution) are obtained by *potentization*.

*Potentization* in this context is the dilution by stages of solid or liquid formulations by the stated Method.

The letter x [D in German usage] is used to designate dilutions made in a ratio of 1:10, the letter c [C in German usage] dilutions made in a ratio of 1:100.

A figure added to the designatory letters 'x' and 'c' refers to the number of dilution stages [*emphasis in the original*].

10. In the section entitled "Manufacture," the GHP describes standard homeopathic preparation technologies for various known homeopathic preparations. For each described method, the GHP describes the necessary potentization methodology.

11. It is my opinion as one well skilled in the art that the meaning of the term "homeopathic activation or potentization" was well defined to one skilled in the art at the time of filing of the '652 application. The disclosure of the attached Exhibit II supports my opinion.

12. It is also my opinion that one skilled in the art would clearly understand the meaning of C12 or C30 in reference to homeopathic dilutions. The disclosure of the attached Exhibit II supports my opinion.

All statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment; or both, under Section 1001 of Title 18 of the U.S. Code and that such willful false statements may jeopardize the validity of any patent application issuing thereon.

Dated: December 10, 2008

A handwritten signature in black ink, consisting of a stylized, cursive letter 'L' with a horizontal line extending to the right.

# **REPORT**

## **DETERMINATION OF ULTRA-LOW DOSES OF ANTIBODIES TO INTERFERON GAMMA ANTIVIRAL EFFICACY AFTER INTRANASAL CHALLENGE WITH A LETHAL DOSE OF INFLUENZA A VIRUS IN BALB/C MICE.**

Influenza A H3N8, ATCC VR 317

Project number: **MMM 011 MO**

Protocol number: **0999**

**Report number: MMM 012 MO/999-03**

Report for:

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Project number : MMM 011 MO  
Report number: MMM 011 MO/0999-02

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### SUMMARY

**Lethal challenge:** 5 LD50 of Influenza A H3N8, A Equi2/Miami /1/63, ATCC VR317 Ref LSP4 dated 12/06/06 were given intranasally on day 1.

**Experimental system:** Female Balb/c mice; 4 groups of 20; observation period 26 days, acclimatization > 10 days.

**Quantity used for testing:** Dosing of test products: 200 µl doses of Materia Medica Sample was given bid per os via gavages, from 5 days prior to the challenge to 26 days after the challenge.  
Positive control used oseltamivir per os at 4 mg/kg/day from day 1 to day 6.  
Negative control distilled water (200 µl bid per os via gavages). One group remained unchallenged.

**Materia Medica Sample:** Ultra-low doses of antibodies to interferon gamma; mixture of homoeopathic dilutions C12, C30, C50. The tested substance is an active ingredient of a therapeutic - anaferon for children .

**Abbreviation of**

**Materia Medica Sample:** ULD of Ab to IFN $\gamma$

**Storage:** Sample was kept at 5 +/- 2 °C until day of use.

**Sample receipt:** Mar 27, 2008

**Protocol signature by:**

- Study Director: Jan 22, 2008

- Sponsor: Jan 21, 2008

**Starting of the experiments:** June 20, 2008

**Completion of the experiments:** July 27, 2008

**Amendment to the protocol:** No

**Deviation to the protocol** Yes : ref. D1

The intranasal infection of female Balb/c mice with  $3 \times 10^8$  TCID<sub>50</sub>/ml Influenza virus (H3N8), strain Equi2/ Miami/1/63 caused the death of 80% of the female Balb/c mice; first signs of infection starting 48 hours after the challenge.

Ultra-low doses of antibodies to interferon gamma in a preventative and curative oral dose regimen were more effective as compared to oseltamivir (4 mg/kg/day), providing statistically significant reduction of the death rate over time. Both experimental and reference treatments reduced infection clinical signs duration and enhanced animals survival when compared to placebo.

Ultra-low doses of antibodies to interferon gamma and oseltamivir were well tolerated by the animals.

The model of lethal infection of mice with influenza A virus showed that ultra-low doses of antibodies to interferon gamma reduce morbidity and mortality of the animals with an efficacy at least equal or exceeding that of oseltamivir. As the predictive value of mice infectious models for human extrapolation is generally accepted, these data support the potential for the effective use of ultra-low doses of antibodies to interferon gamma in humans.

**FIRST PART: GENERAL INFORMATION**

**1. QUALITY ASSURANCE**

**1.1. General information**

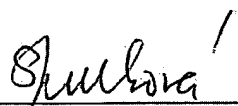
All raw data, an original version of the final protocol and of the final report, and the correspondence between APcis and the sponsor or/and Texcell will be transferred to APcis archives for 5 years. After this period, APcis will contact the sponsor in order to decide whether the file should be sent back at the sponsor's expenses or destroyed.

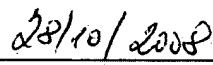
**1.2. Quality assurance statement**

This study was performed under the scientific responsibility of the study director in accordance with Good Laboratory Practice requirements. The study was audited by the Quality Assurance unit.

The dates of the audits were Dec 18, 2007 for study protocol Sept 30, 2008 for data and Oct 09, 2008 for report. No event susceptible to alter or modify the outcome of the study was reported.

I, hereby certify that this final report is representative of the methods used and is an accurate reflection of the data generated during the study.

  
\_\_\_\_\_  
M. SPULKOVA,  
QA Officer

  
\_\_\_\_\_  
Date of signature



## 2. AUTHENTICATION

I, the undersigned, hereby declare that this work was carried out under my direction in accordance with the protocol 0999.

The procedures described in the report correspond to those used for the study, and the report represents a true and accurate record of the results obtained.

  
\_\_\_\_\_  
Jean Pierre TAFANI, DVM, Dipl.ECVPT  
Study Director

Oct 28, 2008  
\_\_\_\_\_  
Date of signature

## **SECOND PART: Influenza virus challenge in Balb/c mice**

### **1. PURPOSE AND GENERAL APPROACH**

The purpose of this study was to determine the efficacy of ULD of Ab to IFN $\gamma$  in mice challenged by 5 x LD50 of Influenza hemagglutinating virus H3N8. The virus H3N8 is known for its ability to cause flu disease in Balb/c mice after intravenous, intratracheal and intranasal inoculations.

In this aim, a titered viral suspension was thawed and inoculated by intranasal and intratracheal route to eight groups of twenty weaned female Balb/c mice (anaesthetized upon inoculation) which were regularly observed for the duration of the test.

Virus sample received on Jan 10, 2008 and April 24, 2008:

H3N8 –ATCC VR-317 ref LSP4 12/06/06

Titer:  $3 \times 10^8$  TCID per ml i.e. circa  $2.1 \times 10^8$  pfu/ml, 8 ml.

Virus inoculum was diluted 1/2 in sterile saline to prepare the lethal challenge doses of  $10^7$  pfu per mouse intranasally.

### **2. MATERIAL**

#### **2.1 SPF Mice**

The weaned female Balb/c mice were received on June 25, 2008 at the average bodyweight of  $12 \pm 2$  g (4-6 weeks) and acclimatized for more than 5 days in the L2 Laboratory (precisely 10 days before challenge). They were randomly assigned to cages (Type P Charles River) of 10 and kept in ventilated cabinets equipped with HEPA filters at  $20 \pm 2^\circ\text{C}$  upon receipt.

**Origin:** CHARLES RIVER Laboratory Italy

Initial (Day -10 = June 20, 2008) bodyweight (BW) averaged  $11.1 \pm 2$  g.

#### **2.2 Vehicle**

Initial viral suspension was diluted in sterile phosphate buffer PBS (Difco). No antibiotic was added.

Reference product Oseltamivir was diluted in NaCl 0,9 p. 100 BRAUN (lot 6037B06 exp date Dec 2008); placebo (negative control) was made of distillate alone, ULD of Ab to IFN $\gamma$  had been prepared in advance by the sponsor.

#### **2.3. Reference product: Oseltamivir**

Oseltamivir was obtained from TAMIFLU 75 mg capsules (ROCHE, UK) batch 8113901, exp date Aug 2010.

**Origin:** ROCHE  
6 Falcon Way, Shire Park  
Welwyn Garden City AL711W, UK.

### **3. METHODS**

Experiment was carried out according to protocol 0999.

#### **3.1. Experimental procedure**

##### **3.1.1. Test article preparation**

Virus was received (multiplied on MDCK cells in Dulbecco's modified Eagle medium supplemented with streptomycin 100 µg/ml and 5% newborn calf serum) from Pasteur Institute via its subsidiary Texcell, 91000 Evry, France and passaged in eggs (EP2).

Production reference was H3N8 –ATCC VR-317 ref LSP4 12/06/06.

In present study, four virus vials were thawed at ambient temperature prior to challenge. A bottle (ref 24620) of 250 ml NaCl was used, not supplemented with gentamicin 1/1000.

50 µl inoculum were prepared for each mouse one hour prior to the challenge. Resulting dilution was gently stirred, sucked into adequate syringes as needed and inoculated with 100 µl pipette tips.

Four 2 ml vials with  $2.1 \times 10^8$  pfu/ml ( $3 \times 10^8$  TCID<sub>50</sub>) were used for this study (S0).

Highest concentration was diluted 1:2 (i.e.  $0.5 \times 10^7$  pfu or  $0.75 \times 10^7$  TCID<sub>50</sub> per 50 µl dose).

##### Experimental product:

ULD of Ab to IFN $\gamma$  were received on Mar 27, 2008 via DHL and kept at  $5 \pm 3^\circ\text{C}$  in the laboratory until use. 10 ml was poured daily from the 250 ml bottle into a sterile PVC tube of 12 ml, identified and kept with 1 ml syringes for gavage. The remainder of the daily aliquots was discarded prior to refill the next day.

Two bottles were used during the trial; the remaining bottle has been kept in same condition ( $5 \pm 3^\circ\text{C}$ ) for one month after completion of the present report and discarded according to the regulations of biotechnology products.

##### **3.1.2. Inoculation of mice**

###### **Intranasal route**

Mice in groups 1 to 3 were exposed to individual inoculation via intranasal route after sedation with 100 µl per 15 g BW of ZOLETIL IP (tiletamine-oxazepam 5 mg/kg).

Inoculations were made aseptically with disposable sterile yellow Eppendorf pipettes.

With a constant volume of 50 µl (half in each nostril) actual doses were thus 3 to 5 LD<sub>50</sub> as determined per MMM011MO experiment.

Inoculations were made on Jun 30, 2008 under a safety cabinet of class II. The mice were inoculated in the order of the groups starting with reference product group. Thus the challenged group treated with placebo was the last group inoculated.

### 3.1.3. Animal housing and maintenance

Mice were held separately for each treatment group in different compartments of an autonomous ventilated cabinet equipped with sterilizing filters and placed into the laboratory L2 room.

Gamma irradiated complete pelleted feed (SAFE, F-89 Augy) was given ad libitum and renewed daily.

Water (Beaupré) was constantly available and renewed daily in glass waterers, also cleaned and disinfected daily, placed in each cage.

PVC cages from Animal Care System for each group of 10 mice, equipped with filters feed reservoir and 250 ml PVC bottle with stainless steel pipette for mice, were identified and sealed with tape and renewed weekly or as needed, with sterile litter made of soft tissues that made an enriched environment for the mice.

### 3.2 Treatment groups

**Table I - Treatment groups**

Days of experiment	1 - 5	6	7 - 11	12 - 32
Days after challenge	(-5) – (-1)	(0) Day of challenge Time of challenge is 11.00 ± 1 hr	(1) – (5)	(6) – (26)
Group 1 Test article group (20 mice)	ULD of Ab to IFN $\gamma$ by oral gavages twice daily (0.2 ml/ mouse per gavage) at 10.00± 1hr and 17.00± 1hr.			
Group 2 Reference group (20 mice)	Placebo by oral gavages twice daily (0.2 ml/ mouse per gavage) at 10.00± 1hr and at 17.00± 1hr	Oseltamivir by oral gavages twice daily at 10.00 ± 1rh and at 17.00 ± 1hr. with first treatment just after challenge (1 hour)	Placebo by oral gavages twice daily (0.2 ml/ mouse per gavage) at 10.00 ± 1hr and at 17.00 ± 1hr	
Group 3 Untreated challenges control group (20 mice)	Placebo by oral gavages twice daily (0.2 ml/ mouse per gavage) at 10.00± 1hr and 17.00± 1hr.			
Group 4 Negative control Group (20 mice)	Unchallenged and untreated group. Received no treatment and no inoculum to monitor reference untreated growth and health patterns.			

#### 4. RESULTS

Results are gathered in Appendix as means and individual data:

- disease occurrence is summarized on **Graph 1** (Tables III and IV),
- mortality on Table V,
- survival rates on **Graphs 2A and 2B** (Table VI),
- morbi-mortality on **Graph 3** (Tables VII and VIII),
- Summarized bodyweight changes :
  - Mean on **Graph 4** (Table IX),
  - Total on **Graph 5** (Table X),
- Individual bodyweight changes on Tables XI. 1. to XI.4.
- Necropsy findings (gross pathology) on Table XII,
- Haematology data :
  - Summarized data on Tables XIII, XIV and XV,
  - Individual data on Tables XVI.1. to XVI.4.

##### 4.1. Clinical observations: health scores and bodyweight changes

###### Health scores:

Mice have been regularly observed during the test by a trained technician (once or twice per day), by cage right after gavage. Results are gathered in tabular form separately for each cage of 10.

Morbidity was assessed once daily as a measure of viral infection according to a binary score system for each mouse based on presence of at least one of the major signs of disease: diarrhoea, respiratory dyspnea or cachexia, as the behavioral usual scale was too dependent from the observer, especially with Balb/c mice that appear shy (death simulating is part of their defense behavior) upon observation. Thus previous scale from 5 = healthy to 0 = dead was abandoned; i.e. 4 = appetite loss or ruffled fur, 3 = sick = malaise, ruffled fur, low motility, 2 = very sick idem + no appetite, dehydration, 1 = moribund).

Sick mice appeared with ruffled fur especially around the head and neck, likely because of altered grooming activity, with respiratory distress (increased respiratory cycle rate).

All unchallenged mice appeared healthy throughout the study.

All mice having received the viral inoculum showed signs of infection at least in a transient manner.

Number of sick mice increased from day 2 to day 9 after challenge (8-15 days after experiment onset) and then decreased in most treated groups before the half of the observation group, while in challenged untreated group a majority of the animals that were alive during the second half of observation period presented cachexia.

Thus ULD of Ab to IFN $\gamma$  significantly reduced the duration of infection signs.. Oseltamivir does not reduce the disease more than ULD of Ab to IFN $\gamma$ ; moreover, until the end of the first week post challenge, the curative effect of the reference

product appears very weak as no difference was noticed with the placebo until Day 9 post challenge, i.e. 2 days after the end of the 6 day treatment.

When sick and dead mice are cumulated on a daily base, the curves of the total: sick + dead per day per group over time show a marked improvement with all treatments compared to the vehicle alone (ANOVA, Dunnett).

**Bodyweight changes:**

Mice were weighted at least twice a week until day 26 after the challenge (the 32 day of experiment), always after 5.00 pm.

Unchallenged untreated mice:

Weight variations in negative controls show on day (-5) (5 days before the challenge i.e. on first day of experiment) a reduced mean and total BW due to an artifact – water and feed availability was reduced on day (-6) because of a cover dysfunction that was replaced on day (-5). From then on, and especially after day 1, the mice reached progressively their adult BW of 20-22g.

Challenged untreated mice (placebo):

From day 6 after the challenge i.e. 12 days after experiment onset, the mean BW began to decrease showing actual weight loss especially within the first week (-2 grams). Total BW decreased throughout the observation period. The last surviving mice tend to stop losing weight at the end of the observation period.

Oseltamivir treated mice:

On day 6 after the challenge (i.e. 12 after experiment onset), the mean BW was as low as the lowest mean BW in the placebo group, suggesting a severe disease onset. From then on, surviving mice tend to gain weight and recover, thus suggesting an antiviral effect of oseltamivir, which appears to enhance the mice defense.

ULD of Ab to IFN $\gamma$  treated mice:

Mean BW of alive mice was constantly a positive function of time in group treated with ULD of Ab to IFN $\gamma$ , while mean BW was above initial (day of challenge) weight in group treated with oseltamivir, and not challenged untreated mice. Thus suggesting evident antiviral activity of ULD of Ab to IFN $\gamma$ .

**4.2. Mortality**

No mouse was found dead within the first 6 days post challenge. Deaths occurred from day 7 to day 21 after the challenge (from day 13 to day 27 after experiment onset), mostly from day 11 to day 16 post challenge (i.e. days 17-22 after experiment onset) in placebo treated mice. The death followed BW loss in all cases. When compared to survival time in previous study MMM010MO, the slightly longer lag time to death in the present study may be attributed to forced drinking during gavage (0.4 ml per day).

Unchallenged untreated mice:

No death occurred in unchallenged untreated mice.

Challenged untreated mice:

Death in negative controls occurred sooner than in treated groups and touched more than half of the mice (80%).

Oseltamivir treated mice:

Deaths occurred in the second week post challenge and struck 25 % of the mice. The curative reference thus prevented about half of the death in the placebo group.

**ULD of Ab to IFN $\gamma$  treated mice:**

Only one mouse died in ULD of Ab to IFN $\gamma$  treated group. Low death rate (5%) and prolonged lag time to death (8 days post challenge) proved high antiviral efficacy of ULD of Ab to IFN $\gamma$ .

Twelve mice per group were necropsied to observe eventual pathology signs. Lung and tracheal tissues of sacrificed mice, although no collection of bronchial secretions with PBS wash according to internal procedure was performed, presented mild inflammatory signs of pneumonia and white spots on the heart suggested pericarditis in more than half of the surviving mice at the end of the observation period (Table XII).

**Table II - Mean life duration by group**

<i>Group</i>	<i>Products</i>	<i>Mean life duration</i>
Group 1	ULD of Ab to IFN $\gamma$	25.05 $\pm$ 0.95 ***
Group 2	Oseltamivir	21.65 $\pm$ 1.76 ***
Group 3	Placebo	13.55 $\pm$ 1.69
Group 4	Unchallenged untreated	26.00 $\pm$ 0.00 ***

\*\*\* p<0.001 vs placebo

#### 4.3. Haematology

Blood samples were obtained from exsanguination of 5 mice per group on Day 26. Blood was withdrawn from heart puncture and samples of 1 ml were centrifuged. Sera were added gentamicin 1 p. 1000 to avoid any bacterial contamination prior to freezing.

Data are gathered per group in Tables XIII (number of cells per mm<sup>3</sup>), XIV and XV, and by individual mouse on Tables XVI.1 to 4.

Red blood cells are unchanged by flu disease, as expected.

Obvious changes in blood formula were recorded between unchallenged untreated mice and challenged plus placebo (4 survivors):

White blood cells were doubled (x 2); their breakdown in Lympho %; Monocytes %, Granulocytes %, Eosinophils % and Basophils % show a relative decrease in Monocytes. Both changes are consistent with a (viral) infection. In the 4 survivors of the challenged untreated group, and in the reference group as well, there is a trend towards a decreased platelet number, suggesting some individuals were cachectic to the point of eventual foreseeable clotting troubles (close to IVDC). Although in mice, platelet counts determined by a coulter are usually low because of induced aggregates, highly correlated to elevated Mega platelet %, these low numbers are suggesting that reference and placebo might have lead to a more severe disease.

There is no change in the breakdown in WBC subclass between placebo and oseltamivir.

None changes were seen with ULD of Ab to IFN $\gamma$  treated mice.



### **CONCLUSION**

The intranasal infection of female Balb/c mice with  $3 \times 10^8$  TCID<sub>50</sub>/ml Influenza virus (H3N8), strain Equi2/ Miami/1/63 caused the death of 80% of the female Balb/c mice; first signs of infection starting 48 hours after the challenge.

Ultra-low doses of antibodies to interferon gamma in a preventative and curative oral dose regimen were more effective as compared to oseltamivir (4 mg/kg/day), providing statistically significant reduction of the death rate over time. Both experimental and reference treatments reduced infection clinical signs duration and enhanced animals survival when compared to placebo.

Ultra-low doses of antibodies to interferon gamma and oseltamivir were well tolerated by the animals.

The model of lethal infection of mice with influenza A virus showed that ultra-low doses of antibodies to interferon gamma reduce morbidity and mortality of the animals with an efficacy at least equal or exceeding that of oseltamivir. As the predictive value of mice infectious models for human extrapolation is generally accepted, these data support the potential for the effective use of ultra-low doses of antibodies to interferon gamma in humans.

### **REFEFENCE**

**Hanshaw D. and Castelman W.** Dept of Infect. Diseases, Univ. Florida, CVM.  
Gainesville. Canine H3N8 Influenza virus infection in mice. 2007.